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Herpes simplex viruses (1 and 2) and varicella-zoster virus infections in an adult population with aseptic meningitis or encephalitis

A nine-year retrospective clinical study

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Abstract

Three α-herpesviruses are known to be associated with central nervous system (CNS) infection; however, there are limited data on the incidence and clinical characteristics of α-herpesviruses CNS infections. This study aimed to assess the clinical manifestations, laboratory findings, and outcomes in patients with human herpes simplex virus 1 (HSV-1), human herpes simplex virus 2 (HSV-2), and varicella-zoster virus (VZV) CNS infections.

We identified cases of HSV-1, HSV-2, and VZV CNS infections and reviewed their clinical and laboratory characteristics. The study population was drawn from patients with HSV-1, HSV-2, and VZV polymerase chain reaction positivity in cerebrospinal fluid (CSF) who visited Pusan National University Hospital between 2010 and 2018.

During the 9-year study period, a total of 727 CSF samples were examined, with 72.2% (525/727) patients identified as having a CNS infection. Of 471 patients with aseptic meningitis and encephalitis, the causative virus was identified in 145 patients, and no virus was detected in 337 patients. A total of 15.2% (80/525) were diagnosed with one of the 3 herpesviruses as causative agents, 59 patients had meningitis, and 21 patients had encephalitis. Eleven patients with HSV-1, 27 patients with HSV-2, and 42 patients with VZV CNS infections were included. The distribution of cases by age showed different patterns depending on the type of herpesvirus infection. Compared with the HSV-1 group, the median age in the HSV-2 group was younger (HSV-1: 58 years; HSV-2: 38 years; $P = .004$), and patients with VZV infections showed a bimodal age distribution. Encephalitis was more common in the HSV-1 group, and HSV-1 infection was associated with a poor prognosis at discharge. CSF white blood cell counts were significantly lower in patients infected with HSV-1 (117×10^6 cells/L) than in patients infected with VZV (301×10^6 cells/L) ($P = .008$).

These 3 herpesviruses are important causes of CNS infections regardless of immunologic status. HSV-1 infection was commonly associated with encephalitis and poor prognosis; HSV-2 and VZV CNS infections were associated with a low risk of mortality and neurological sequelae.

Abbreviations: ADA = adenosine deaminase, CNS = central nervous system, CRP = C-reactive protein, CSF = cerebrospinal fluid, HSV-1 = herpes simplex viruses 1, HSV-2 = herpes simplex viruses 2, IQR = interquartile range, PCR = polymerase chain reaction, VZV = varicella-zoster virus, WBC = white blood cell.

Keywords: central nervous system, cerebrospinal fluid, herpes simplex viruses, infections, varicella-zoster virus

1. Introduction

Three α-herpesviruses, human herpes simplex viruses 1, 2 (human herpesvirus 1, 2: HSV-1, HSV-2) and the varicella-zoster virus (VZV; human herpesvirus 3), are known to be associated with central nervous system (CNS) infections in adults and are responsible for significant neurological morbidity and mortality.[1] Clinical symptoms and disease prognosis depend on the specific infectious agents and the immunologic state of the host.[1]

The development of polymerase chain reaction (PCR) technology has enabled the molecular detection of viral genomes and is increasingly being used in routine clinical practice. The use of PCR widens the knowledge about HSV-1, HSV-2, and VZV infections in the CNS,[2] providing a rapid and accurate diagnosis that enables the use of antiviral treatment in patients with meningitis and encephalitis.[3] It is known that HSV-1 infection usually establishes latency in the trigeminal ganglion and causes encephalitic illness, while HSV-2 infection usually establishes latency in the sacral sensory ganglia and typically results in meningitis-type illness. VZV infection establishes latency in any dorsal root ganglion; it is known that VZV reactivation is seldom associated with clinical CNS infection.[4] Until recently, however,

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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there have been limited data on the incidence and clinical findings of CNS infection associated with herpesviruses. Since early antiviral therapy could be beneficial to patients afflicted with herpesviruses CNS infection, a greater understanding of the etiology and clinical characteristics is needed.

Thus, this study aimed to assess the clinical manifestations, outcomes, and laboratory findings in patients with HSV-1, HSV-2, and VZV CNS infections. Understanding the differences between CNS infections from herpesviruses might assist clinicians in their investigations and guide therapeutic decisions for the treatment of patients presenting with CNS infection.

2. Methods

2.1. Characteristics of the study population

This retrospective study was performed at the Pusan National University Hospital in Pusan, the Republic of Korea, between January 2010 and December 2018. The study population was comprised of adults (≥16 years old) whose cerebrospinal fluid (CSF) samples were obtained for HSV-1, HSV-2, and VZV detection using PCR methods following presentation at the emergency department with the clinical suspicion of CNS infection (see Section 2.4). Patients whose clinical presentation was indicative of CNS infection and who had a positive CSF PCR result for HSV-1, HSV-2, or VZV were considered to have had a confirmed infection.

2.2. Data acquisition

A standardized data form was made, and the data were obtained from patient medical electronic records. Variables included in the database were: age, sex, underlying disease, laboratory data, brain imaging results, clinical manifestations (skin rash or cranial nerve paralysis), usage of intravenous acyclovir, and clinical outcome. We reviewed the clinical and laboratory records as well as the radiologist's statements of brain imaging done at the time DNA positivity in CSF. The clinical outcomes were measured by in-hospital crude mortality data and the presence of neurologic sequelae at discharge.

2.3. Ethical declaration

The study protocol was approved by the Institutional Review Board Committee of the Pusan National University Hospital, Pusan, Republic of Korea (1911-006-084). Informed consent was waived by the Institutional Review Board owing to the retrospective nature of the study.

2.4. Definitions of CNS infection

The inclusion criteria for aseptic meningitis as follows: patients with symptoms such as headache, neck stiffness, and fever, patients with CSF white blood cell (WBC) counts $\geq 5 \times 10^6$/L, without evidence of cerebral dysfunction, such as altered mental status, seizure or focal neurologic deficit.[5] The inclusion criteria for encephalitis as follows: patients with encephalopathy (altered mental status, lethargy, or change in personality); with at least one of the following symptoms: fever, seizure, focal neurologic deficit, CSF pleocytosis, or electroencephalography or neuroimaging findings consistent with encephalitis.[5] Patients with CSF tests suggesting bacterial meningitis or those with evidence of other disease etiology were excluded.

2.5. Laboratory data

Data of CSF and blood samples within the first 24 hours of admission were collected. We obtained results of laboratory tests available in the electronic medical records. Blood: glucose, sodium, potassium, C-reactive protein (CRP) levels, and WBC count, CSF: glucose, protein, adenosine deaminase (ADA) levels, WBC count, lymphocytes, and neutrophil percentages; HSV-1, HSV-2, and VZV CSF PCR. In our institution, total DNA was extracted from CSF samples using the Roche MagNa Pure 96 DNA and Viral NA Small Volume Kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions. The PCR reactions were conducted by qualitative PCR tests for HSV-1 (Real-Q HSV I detection Kit, Biosewoom, Republic of Korea), HSV-2 (Real-Q HSV II detection Kit, Biosewoom, Republic of Korea), and VZV (VZV PCR Kit, Biocore, Republic of Korea), according to the manufacturers' instructions.

2.6. Statistical Analysis

Statistical analysis was performed using the MedCalc Statistical Software version 19.1 (MedCalc Software, Ostend, Belgium). Quantitative variables were expressed as the median with interquartile range (IQR) due to the nonparametric distribution, while qualitative variables were expressed as numbers and percentages. Chi-square tests (or Fisher exact tests, where appropriate) and Kruskal–Wallis test were used to compare the differences between each viral infection. Dunn test was applied for posthoc analysis of between-group. P-values $<.05$ were considered to be statistically significant.

3. Results

3.1. Patient characteristics and clinical diagnosis (Fig. 1)

During the 9-year study period, 727 people (414 males and 313 females) were evaluated in the emergency department, with a median age of 49 years (range: 17–92 years, IQR: 32–64 years). Of these, 525 (72.2%, 525/727) patients were identified as having a CNS infection. One hundred seventy-eight patients were excluded because they did not meet the diagnostic criteria for CNS infection, and 24 patients were excluded due to diagnosis of other diseases such as leptomeningeal seeding, autoimmune disease, myelitis, etc. Three hundred twenty-eight (62.5%, 328/525) patients were identified as having aseptic meningitis, while 29.3% (154/525) patients were identified as having encephalitis. Of the total 328 patients with aseptic meningitis, 1 (0.3%, 1/328) were infected with HSV-1, 23 (7.0%, 23/328) with HSV-2, 35 (10.6%, 35/328) with VZV, 13 (4.0%, 13/328) with Epstein–Barr virus, 4 (1.2%, 4/328) with cytomegalovirus, 8 (2.4%, 8/328) with enterovirus and 3 (0.9%, 3/328) with Haantan virus. In 241 (73.5%%, 241/328) patients, causative agents were not found. Of 154 patients with encephalitis, 10 (6.5%, 10/154) were infected with HSV-1, 4 (2.6%, 4/154) with HSV-2, 7 (4.5%, 7/154) with VZV, 8 (5.2%, 8/154) with Epstein–Barr virus and one each with cytomegalovirus and Haantan virus. No virus was detected in 123 (79.9%, 123/154) patients (Fig. 1).

3.2. Demographic characteristics of patients infected with HSV-1, HSV-2, and VZV (Figs. 2 and 3, Table 1)

, A total of 80 (15.2%, 80/525) patients were diagnosed with one of the three herpesviruses as causative agents of their aseptic

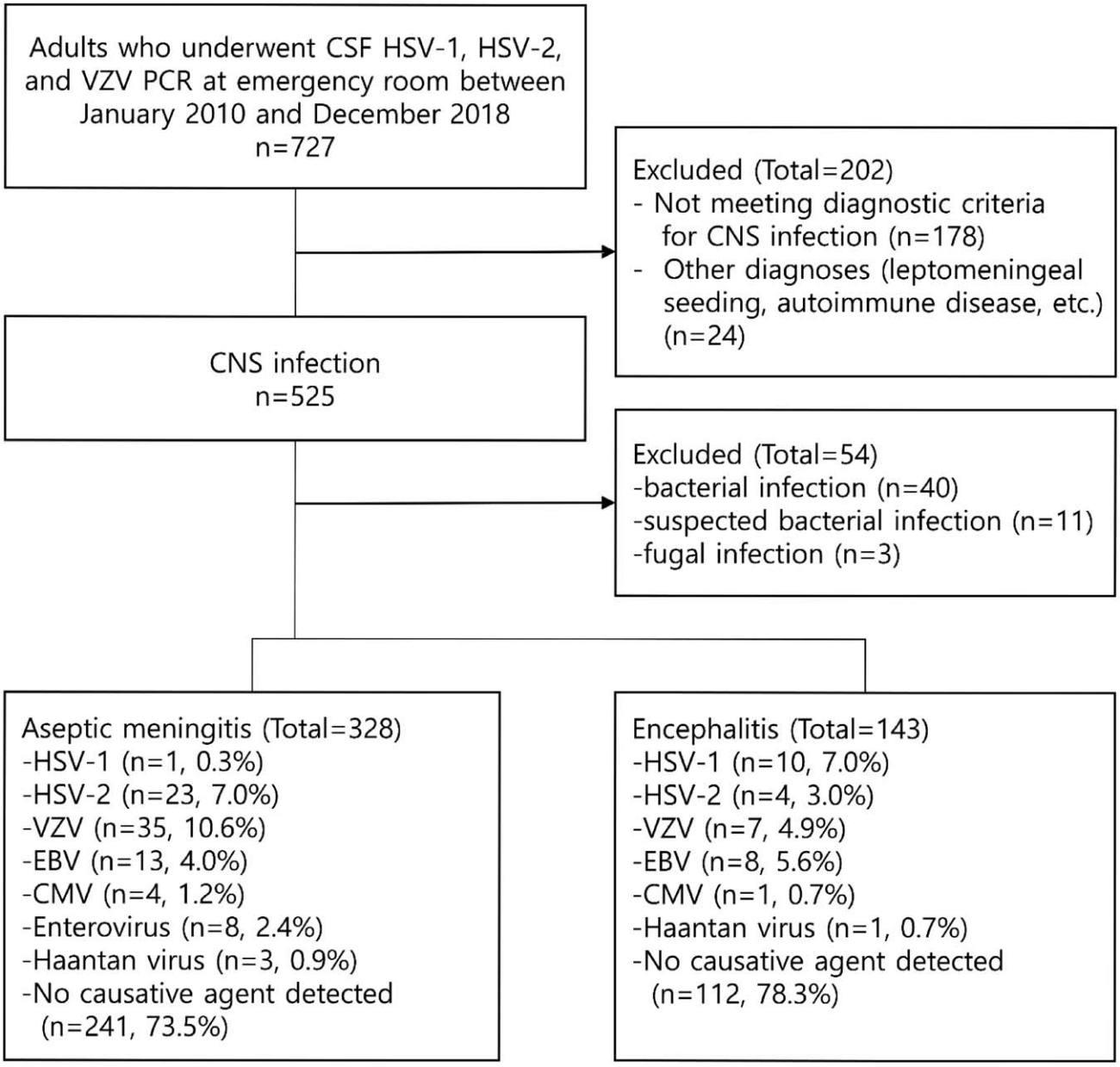

Figure 1. Study flow sheet. Of the 727 evaluated, 525 had a confirmed CNS infection. There were 328 cases of aseptic meningitis and 154 cases of encephalitis. A total of 80 patients were diagnosed with one of the 3 herpesviruses as causative agents. Eleven patients were identified with HSV-1, 27 patients with HSV-2, and 42 patients with VZV. CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, EBV = Epstein–Barr virus, HSV = herpes simplex viruses, PCR = polymerase chain reaction, VZV = varicella-zoster virus.

Table 1

Demographic and clinical characteristics for 80 patients positive for HSV-1, HSV-2, or VZV by CSF PCR.

Demographic and Clinical Characteristics	HSV-1 (n=11)	HSV-2 (n=27)	VZV (n=42)	*P*-value
Age, yr, median (range)	58 (40–65)	38 (27–50)	41 (27–66)	.046
Sex, number, (male: female)	5:6	17:10	29:13	.348
Encephalitis, n (%)	10 (90.9%)	4 (14.8%)	7 (16.7%)	<.001
Abnormal imaging, n (%)	10 (90.9%)	2 (7.4%)	2 (4.8%)	<.001
ICU care, n (%)	8 (72.7%)	1 (3.7%)	5 (11.9%)	<.001
Immunocompromised patients, n (%)	0	1 (3.7%)	3 (7.1%)	.583
IV acyclovir therapy, n (%)	10 (90.9%)	10 (37.0%)	27 (64.3%)	.012
Skin rash, n (%)	0	0	18 (42.9%)	<.001
Poor prognosis at discharge, n (%)	3 (27.3%)	0	3 (7.1%)	.037

CSF = cerebrospinal fluid, HSV = herpes simplex virus, ICU = intensive care unit, IV = intravenous, PCR = polymerase chain reaction, VZV = varicella zoster virus.

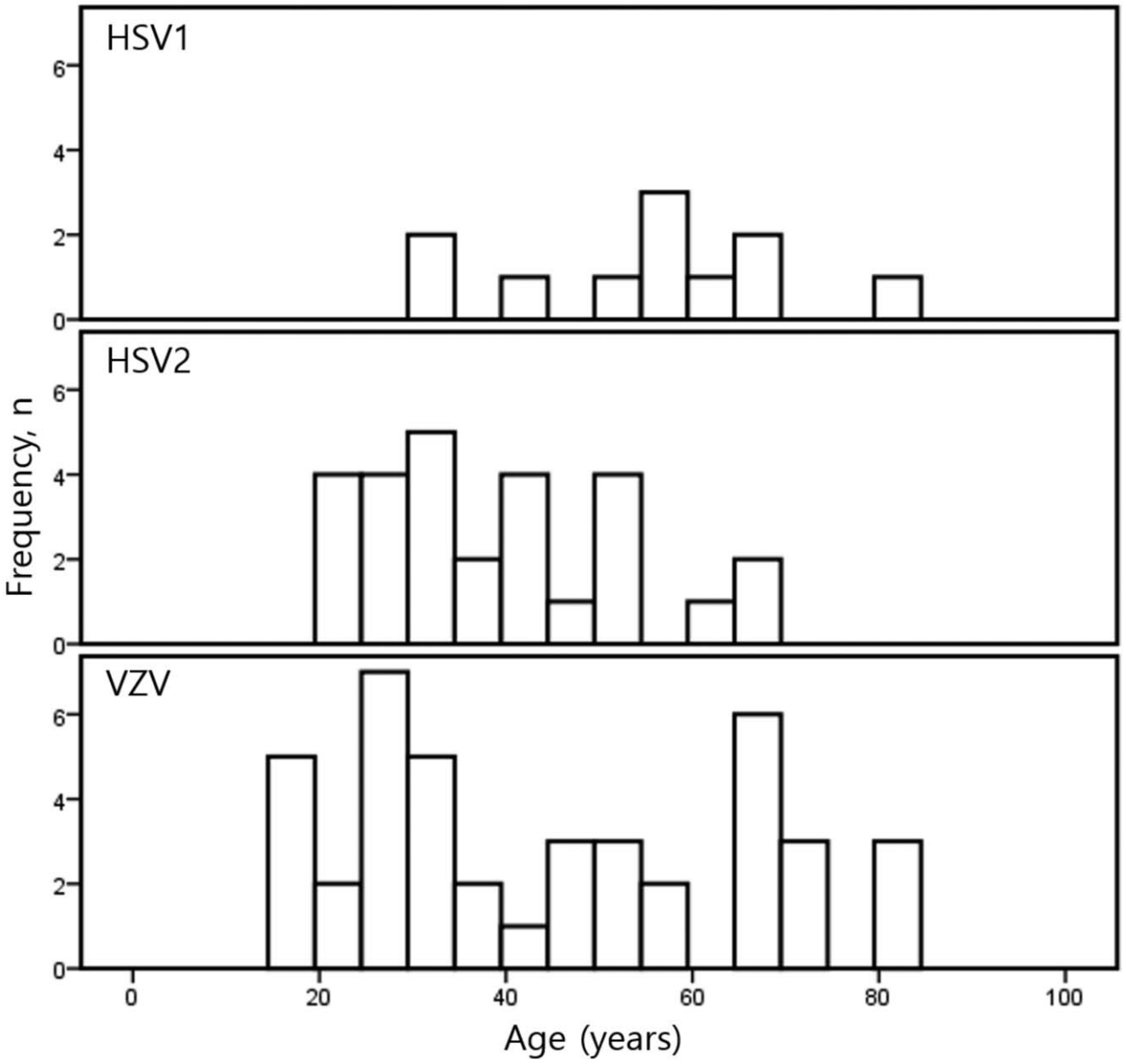

Figure 2. Age distribution of central nervous system (CNS) infections with herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), and varicella-zoster virus (VZV). The age distribution showed different patterns depending on the type of herpesvirus. HSV-1 infection presented in 50 to 60 years of age, whereas HSV-2 infection presented within the 20s to 40s. VZV infections showed a bimodal age distribution.

meningitis or encephalitis. Fifty-one (63.7%, 51/80) of these 80 patients were male, and 29 patients (36.3%, 29/80) were female. Eleven (13.8%, 11/80) patients were identified with HSV-1, 33.8% (27/80) patients with HSV-2, and 52.5% (42/80) patients with VZV. The age distribution showed different patterns depending on the type of herpesvirus infection (Fig. 2) causing the illness. Most patients with HSV-2 infection presented within their 20s to 40s, whereas patients with HSV-1 infection presented mostly in patients 50 to 60 years of age. Compared with the HSV-1 group, the median age in the HSV-2 group was younger (for HSV-1: 58 years [IQR: 40–65]; for. HSV-2: 38 years [IQR: 27–50]; $P = .004$) (Table 1). Patients with VZV infections showed a bimodal age distribution, with the first peak in the 20s and 30s and the second peak in the 70s (Fig. 2). The distribution of cases by seasons of the year was different, but it is not statistically significant (Fig. 3); HSV-1 cases occurred predominantly during the summer months, whereas HSV-2 and VZV cases were identified throughout the year.

3.3. Clinical manifestations of patients infected with HSV-1, HSV-2, and VZV (Table 1)

Based on the clinical features and laboratory data of the 80 patients infected with one of the three herpesviruses, 59 patients had meningitis, and 21 patients had encephalitis. The most common clinical diagnosis in HSV-1-affected patients was encephalitis, but a diagnosis of aseptic meningitis was more commonly associated with the HSV-2 and VZV groups; these diagnoses differed significantly among the three herpesvirus groups ($P < .001$; Table 1). The majority of patients had no

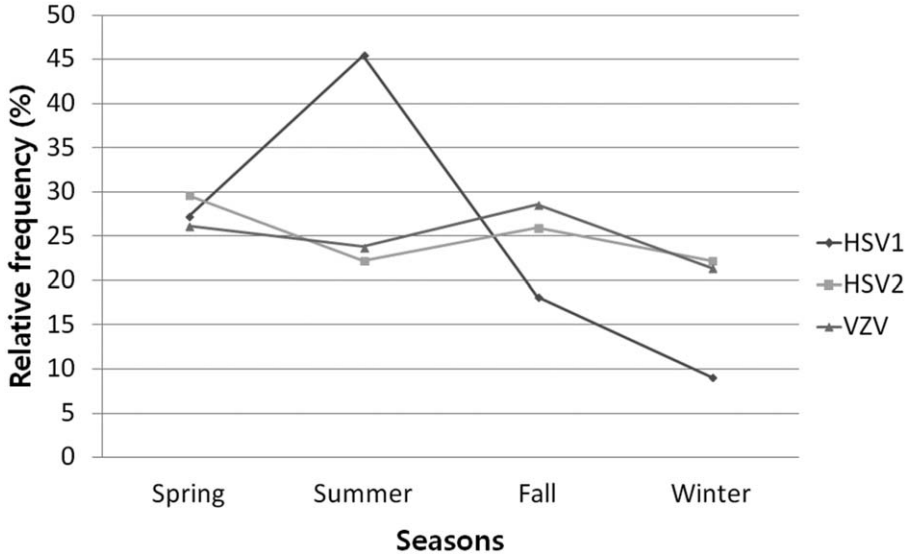

Figure 3. Seasonal distribution of central nervous system (CNS) infections with herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), and varicella-zoster virus (VZV). HSV-1 infection occurred predominantly during the summer, whereas HSV-2 and VZV infection occurred throughout the year.

significant underlying disease and only a few patients were classified as being immunocompromised (HSV-1: n = 0 [0.0%. 0/11]; HSV-2: n = 1 [3.7%, 3/27]; VZV: n = 3 [7.1%, 3/42], $P = .583$; Table 1). Intensive care unit admission in the HSV-1 group was frequent (8/11 patients: 72.7%) but was rarely required in the HSV-2 (1/27 patients: 3.7%) and VZV (2/42 patients: 4.8%) groups and differed significantly among the 3 herpesvirus groups ($P < .001$). Among the affected 80 patients, 47 patients (58.8%, 47/80) received intravenous acyclovir therapy: 90.9% (10/11) patients with HSV-1, 37.0% (10/27) with HSV-2, and 64.3% (27/42) with VZV received intravenous acyclovir therapy, the frequency of which differed significantly between groups ($P = .005$). Presence of severe neurological sequelae at discharge were significantly more frequent in the HSV-1 group (in 3/11 patients: 27.3%) than HSV-2 (in 0/27 patients: 0%) and VZV (in 3/42 patients: 7.1%) groups ($P = .037$). Among the 42 patients infected with VZV, skin rashes were observed in 18 patients (42.9%) (Table 1). There was no skin rash in patients infected with HSV-1 and HSV-2. Disseminated VZV infection was observed in 4.8% (2/42) cases. Cranial nerves were affected only in the VZV group. Four patients were diagnosed with Ramsay Hunt syndrome, and three had cranial nerve X palsy.

3.4. Laboratory findings of patients infected with HSV-1, HSV-2, and VZV (Fig. 4, Table 2)

, Despite the small numbers of patients, the median CSF WBC count was significantly lower in patients infected with HSV-1 (117×10^6 cells/L) than in patients infected with VZV (301×10^6 cells/L) ($P = .008$) (Fig. 4A). No significant differences were found between median CSF WBC counts for HSV-1 and HSV-2 infections. CSF protein levels were highest in the VZV group (115.5 mg/dL) (Fig. 4B). CSF ADA levels were similar in all three groups, but 6 patients infected with VZV and 1 patient infected with HSV-2 had ADA levels above 10 IU/L (Fig. 4C). Serum sodium levels were significantly lower in patients infected with HSV-1 (136.6 mmol/L) than in patients infected with VZV (139.2 mmol/L) ($P = .011$). Hyponatremia occurred frequently in the HSV-1 group (in 5/11 patients: 45.5%), but was rare in the HSV-2 (in 3/27 patients: 11.1%) and VZV (in 5/42 patients: 11.9%) groups ($P = .018$). However, when only encephalitis patients were stratified, serum sodium levels did not differ between groups (HSV-1: 135.8 mmol/L, IQR [130.4–138.3]; HSV-2: 133.6 mmol/L [130.7–138.2]; VZV: 141.5 mmol/L [131.5–145.8]; $P = .42$), nor did frequency of hyponatremia (HSV-1: 5/10 patients [50%]; HSV-2: 3/4 patients (75%); VZV: 3/7 patients (43%); $P = .57$). Serum CRP levels were low overall (median <1 mg/dL), and serum CRP and WBC counts were not significantly different among the three groups ($P = .728$) (Fig. 4D).

3.5. Neuroimaging findings of patients infected with HSV-1, HSV-2, and VZV

Neuroimaging data were available for all patients, with computed tomography scans in all and magnetic resonance imaging (MRI) in 78 (97.5%, 78/80) patients. Abnormal high signal intensity lesions were found in 14 of 78 (17.9%) patients on T2-weighted and fluid-attenuated inversion recovery images of MRI. Among the 14 patients with abnormal findings on neuroimaging, 10 patients were infected with HSV-1, and 2 patients were infected with HSV-2 and VZV, respectively (Table 1). Ninety-one percent (10/11) of patients infected with HSV-1 showed abnormal findings on neuroimaging, of which 4 showed unilateral temporal lobe lesions, 4 showed unilateral insular and temporal lobe lesions, and 2 showed bilateral temporal lobe lesions. Two (7.4%, 2/27) patients with HSV-2 showed high signal intensity in the unilateral temporal lobe on T2-weighted images. Of 2 (4.8%, 2/42) patients with VZV who showed abnormal findings on MRI, 1 showed multifocal nodular enhancement on T1 enhanced images. Another patient showed high signal intensity with hemorrhagic transformation in the left inferior frontal lobe and temporal lobe (Table 1).

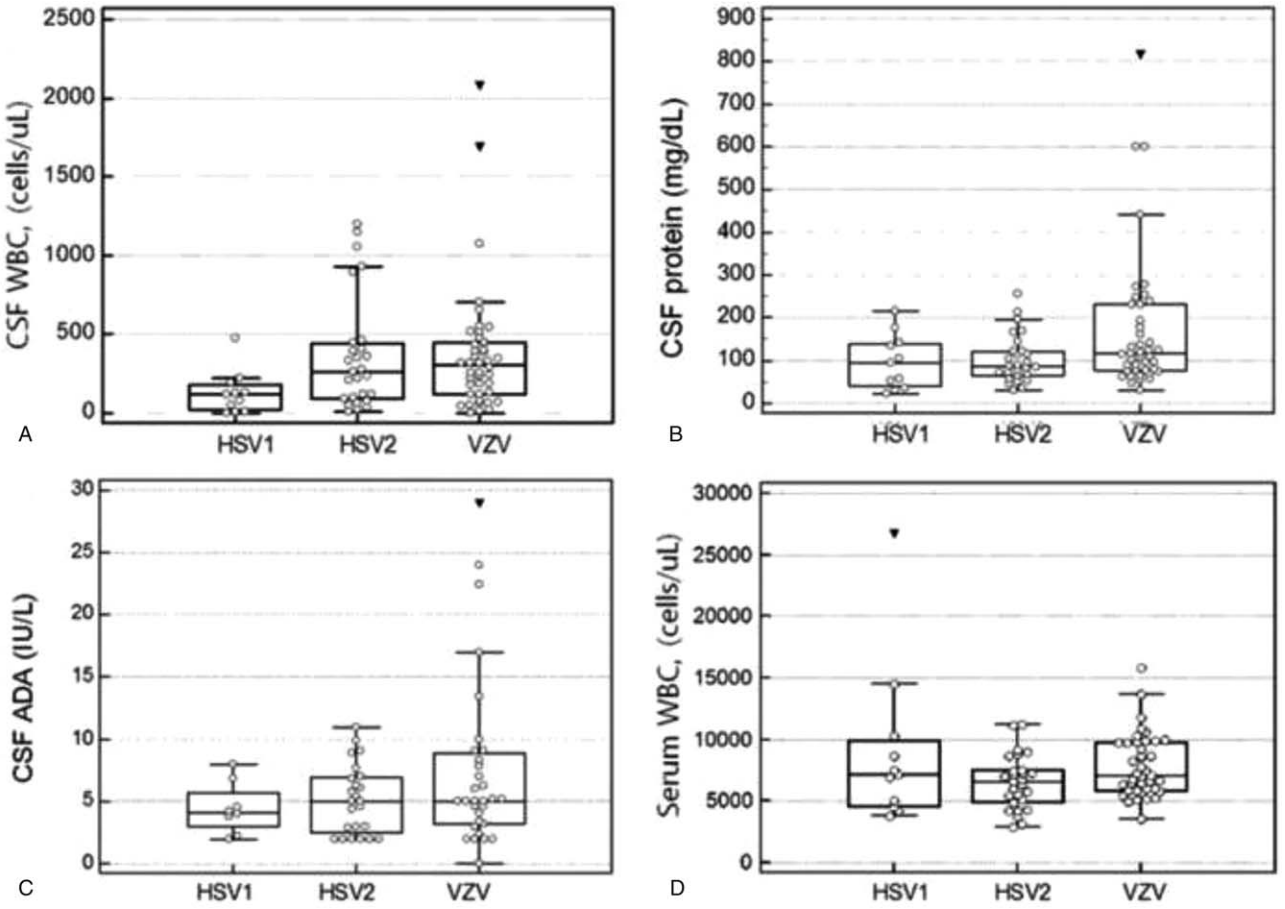

Figure 4. Laboratory findings in CSF and serum. (A) CSF WBC count was significantly lower in patients infected with HSV-1 than those infected with VZV. (B) CSF protein levels were significantly highest in the VZV group. (C) CSF ADA levels were similar, but 6 VZV patients and 1 HSV-2 patient had ADA levels above 10 IU/L. (D) Serum WBC counts were not significantly different. Median and corresponding interquartile ranges of laboratory parameters (A: CSF WBC, B: CSF protein, C: CSF ADA, D: Serum WBC). ADA = adenosine deaminase, CSF = cerebrospinal fluid, HSV-1 = herpes simplex virus 1, HSV-2 = herpes simplex virus 2, VZV = varicella-zoster virus, WBC = white blood cell.

4. Discussion

This study retrospectively analyzed patient demographic and clinical data associated with 3 α-herpesviruses, including HSV-1, HSV-2, and VZV, in patients who presented with aseptic meningitis or encephalitis to the emergency department of a tertiary referral hospital in Pusan, Republic of Korea. Over the 9 years, the 3 herpesviruses' identification rate was 15.3% (80/525). This incidence rate was similar to the results of previous studies (7%∼18%) in adults.[6–8] In our research, VZV was the most common causative herpesvirus of CNS infection, followed by

Table 2

Laboratory findings for 80 patients positive for HSV-1, HSV-2, or VZV by CSF PCR.

Laboratory Findings	HSV-1 (n = 11)	HSV-2 (n = 27)	VZV (n = 42)	*P*-value
CSF WBC count, cells/mm^3, median (IQR)	117 (8–191)	264 (88–450)	302 (118–455)	.034
CSF lymphocytes, %, median (IQR)	80 (57–95)	88 (82–93)	85 (57–93)	.372
CSF neutrophil, %, median (IQR)	8 (0–20)	2 (0–4)	0 (0–5)	.043
CSF protein level, mg/dL, median (IQR)	93.6 (34.5–140.8)	88.0 (63.6–122.7)	115.5 (76.3–230.9)	.313
CSF glucose level, mg/dL, median (IQR)	68 (44–91)	54 (45–62)	52.5 (48–69.3)	.238
Glucose ratio (CSF/serum), median (IQR)	0.56 (0.46–0.68)	0.52 (0.43–0.57)	0.51 (0.43–0.57)	.293
CSF ADA, IU/L, median (IQR)	4.1 (2.6–6.2)	5.0 (2.2–7.0)	5.0 (3.2–9.1)	.407
Hyponatremia (serum Na < 135 mmol/L), n (%)	5 (45.5%)	3 (11.1%)	5 (11.9%)	.018
Serum Na, mmol/L, median (IQR)*	136.6 (130.4–138.3)	138.4 (135.9–140–4)	139.2 (136.1–141.1)	.034
Serum K, mmol/L, median (IQR)	3.64 (3.40–4.06)	4.05 (3.82–4.28)	4.08 (3.80–4.26)	.062
Serum WBC, l/uL, median (IQR)	7151 (4500–10,340)	6610 (4850–7530)	7065 (5810–9760)	.213
Serum CRP, mg/dL, median (IQR)	0.14 (0.05–0.64)	0.11 (0.06–0.70)	0.10 (0.04–0.30)	.728

ADA = adenosine deaminase, CRP = C-reactive protein, CSF = cerebrospinal fluid, HSV = herpes simplex virus, IQR = interquartile range, PCR = polymerase chain reaction, VZV = varicella zoster virus, WBC = white blood cell.

HSV-2. This finding was consistent with what was reported by earlier studies.[9,10] However, some studies reported HSV-2 as the most frequent herpesvirus causing CNS infection.[11,12] This difference in frequency of viral etiologies in CNS infections may be due to climatic differences in the studied regions, cultural differences in sexual behavior of different populations, or genetic susceptibility between ethnic groups.

Most patients with HSV-2 infection presented within their 20s to 40s, whereas patients with HSV-1 infection presented mostly in patients 50 to 60 years of age. Similar to our study, previous studies have shown that patients infected with HSV-2 are younger and have less encephalitis than those infected with HSV-1.[1] Patients with VZV infections showed a bimodal age distribution, with the first peak in the 20s and 30s and the second peak in the 70s (Fig. 2). VZV reactivation occurs mainly in the elderly. Twenty-one (50%, 21/42) patients infected with VZV who were under 40 years of age had no underlying disease; therefore, it is difficult to explain the peak observed in young adults. Two previous studies have also reported that VZV CNS infection is relatively common in relatively young, immunocompetent patients.[13,14] These findings suggest that VZV should be included as a potential cause of CNS infection in immunocompetent young adults. Although more patients (45.5%, 5/11) were hospitalized in the summer, there was no statistically significant seasonal predominance of HSV-1 CNS infection. Since the number of patients infected with HSV-1 in our study was small, more data collection is required. Unlike enterovirus CNS infection, which is known to occur mainly in summer, HSV-1 CNS infection is known to have no specific seasonal distribution.[15,16]

The typical CSF profile of viral meningitis includes lymphocytic pleocytosis (25–500 cells/mL), normal or slightly elevated protein concentration (20–80 mg/dL), and normal glucose concentration.[17] However, we noted that WBC counts were increased over 500 cells/mL in 14 of the 80 patients: 6 (22.2%, 6/27) with HSV-2 and 8 (19.0%, 8/42) with VZV. Patients with VZV infection had significantly higher WBC counts in their CSF than did patients with HSV-1 infection, which is comparable to the results observed in a previous study.[4] Nevertheless, CSF pleocytosis alone could not be used to differentiate between the various etiologies of aseptic meningitis; besides, relatively high CSF protein levels were seen in patients with herpesvirus infections. Fifty-two patients (65%, 52/80) had CSF protein levels over 80 mg/dL; the median protein levels were 102.4 mg/dL (IQR: 69.2–162.6 mg/dL). CSF protein levels were highest in the VZV group. The CSF ADA concentration is used to differentiate between nontuberculous and tubercular meningitis, the latter of which is indicated by concentrations above 10 IU/L.[18,19] The median CSF ADA concentration was low (5 IU/L, [3.0–7.5]), but CSF ADA levels were above 10 IU/L in 7 patients, mostly in the VZV group. Especially in VZV infection, tuberculosis should always be considered in the differential diagnosis of lymphocytic meningitis. Rapid and sensitive diagnostic methods such as CSF PCR are required for adequate and rapid treatment.

Serum sodium levels were significantly lower in patients with HSV-1 infection than those infected by VZV; hyponatremia was present in 45.5% (5/11) of patients with HSV-1, but only in 11.1% (3/27) and 11.9% (5/42) of patients with HSV-2 and VZV-induced viral encephalitis, respectively ($P = .018$). However, when only encephalitis patients were stratified, serum sodium level ($P = .42$) and frequency of hyponatremia ($P = .57$) did not differ between groups. Although hyponatremia was most frequently presented following HSV-1 infection, it was thought that sodium levels decreased with any kind of infectious encephalitis, not due to HSV-1 infection.[20] A previous study of aseptic meningitis showed that CRP levels seldom exceeded 5 mg/dL in patients with viral infection.[21] In our study, CRP levels increased to 5 mg/dL in only 5 (6.3%, 5/80) out of 80 patients.

VZV has a long viral incubation period in the ganglia, and after several decades it can be reactivated and manifests as herpes zoster.[22,23] Herpes zoster is characterized by painful skin rashes with the vesicular eruption in 1 or 2 adjacent dermatomes; it is a common clinical manifestation in adults, especially in the elderly and immunocompromised patients. In this study, more than half of the patients infected with VZV (57%, 24/42) did not have any skin rashes that could suggest herpes zoster. VZV CNS infections have been reported to occur without any skin rashes in 44% to 68% of cases.[24–26] This indicates that the absence of cutaneous lesions does not rule out the possibility of VZV CNS infection. Patients infected with HSV-1 and HSV-2 did not have a skin rash on any part of their bodies, including the mouth and genitals. Of 80 patients with HSV1, HSV-2, and VZV, 58.8% (47/80) received intravenous acyclovir therapy. Most HSV-1 patients were treated with acyclovir, but only 37.0% (10/27) of HSV-2 patients and 64.3% (27/42) of VZV patients received intravenous acyclovir therapy. At admission, we administered intravenous acyclovir therapy only if encephalitis was suspected or there were rashes suggestive of VZV. In the case of aseptic meningitis, not encephalitis, only conservative treatment was performed without acyclovir treatment. Because PCR test takes several days, in patients infected with HSV-2 and VZV who showed only meningitis symptoms, PCR results are often confirmed after symptom improvement, so some patients did not receive acyclovir treatment.

A typical brain MRI finding in patients infected with HSV-1 is asymmetric high signal intensity in the temporal, inferior frontal, and insula lobes on T2-weighted images.[27,28] In our study, all patients with HSV-1 except for one showed these findings. In the 1 patient with normal MRI findings, the clinical diagnosis was meningitis, and there were no other neurological symptoms other than headache. There are few reports of neuroimaging findings in HSV-2 encephalitis. Still, it is reported that they are milder and inconsistent than those of HSV-1 encephalitis; about 80% of patients with HSV-2 encephalitis had high signal intensities with cortical involvement on T2-weighted imaging, of which 40% reported temporal lobe involvement.[27] In our study, 2 out of 4 patients with HSV-2 encephalitis showed high signal intensity in the unilateral temporal lobe on T2-weighted images. Unlike HSV-1 encephalitis, the lesions of VZV encephalitis are not limited to the surrounding area of the temporal lobe, located in multiple areas, and often accompany hemorrhagic or ischemic complications due to vasculopathy.[29,30] Among 7 patients with VZV encephalitis in this study, 2 patients showed abnormal MRI findings. One patient showed multifocal nodular enhancement in the bilateral hemispheres on T1-weighted images. The other patient showed high signal intensity with hemorrhagic transformation in the left inferior frontal and temporal lobes on T2-weighted images.

In the HSV-1 group, encephalitis and poor prognosis at discharge were more common than in the HSV-2 and the VZV groups. Among patients with parenchymal involvement in the brain, 10 patients infected with HSV-1, 2 patients infected with HSV-2, and 2 patients infected with VZV were identified. Most of the patients with HSV-2 and VZV infections, including the 11 patients with encephalitis, had favorable outcomes.

This study had several limitations. Viral load measures were not performed in the laboratory. Therefore, the relationship between viral load and disease severity could not be determined. Second, this study was performed at a single center and was retrospective; the results cannot be generalized. Third, several studies reported that CSF herpesviruses were detected in autoimmune encephalitis,[31] so this study may also include cases of autoimmune encephalitis. Finally, data related to other viruses, such as human enteroviruses and arboviruses, were not included.

This retrospective review of data over a 9-year period has revealed a characteristic pattern of infection and CSF findings in herpesvirus infection cases. Three α-herpesviruses are important causative agents in CNS infectious diseases, regardless of immunologic status. HSV-1 infection was commonly associated with encephalitis and poor prognosis. Compared with HSV-1 CNS infection, HSV-2, and VZV CNS infections were associated with a low risk of mortality and neurological sequelae. Well-designed prospective studies are required further to describe the clinical features and outcomes of herpesvirus infections. The role of intravenous acyclovir is well-established in the treatment of HSV-1 encephalitis, but prospective controlled studies are needed to determine its value in the treatment of CNS infection caused by herpesviruses.

Author contributions

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References

[1] Steiner I, Kennedy PG, Pachner AR. The neurotropic herpes viruses: herpes simplex and varicella-zoster. Lancet Neurol 2007;6:1015–28.
[2] Tang YW. Laboratory diagnosis of CNS infections by molecular amplification techniques. Expert Opin Med Diagn 2007;1:489–509.
[3] Bergstrom T, Alestig K. Treatment of primary and recurrent herpes simplex virus type 2 induced meningitis with acyclovir. Scand J Infect Dis 1990;22:239–40.
[4] Ihekwaba UK, Kudesia G, McKendrick MW. Clinical features of viral meningitis in adults: significant differences in cerebrospinal fluid findings among herpes simplex virus, varicella zoster virus, and enterovirus infections. Clin Infect Dis 2008;47:783–9.
[5] Glaser CA, Gilliam S, Schnurr D, et al. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998-2000. Clin Infect Dis 2003;36:731–42.
[6] Choi R, Kim GM, Jo IJ, et al. Incidence and clinical features of herpes simplex viruses (1 and 2) and varicella-zoster virus infections in an adult Korean population with aseptic meningitis or encephalitis. J Med Virol 2014;86:957–62.
[7] Papa A, Papadopoulou E. Acute viral infections of the central nervous system, 2014–2016, Greece. J Med Virol 2018;90:644–7.
[8] Ben Abid F, Abukhattab M, Ghazouani H, et al. Epidemiology and clinical outcomes of viral central nervous system infections. Int J Infect Dis 2018;73:85–90.
[9] Frantzidou F, Kamaria F, Dumaidi K, Skoura L, Antoniadis A, Papa A. Aseptic meningitis and encephalitis because of herpesviruses and enteroviruses in an immunocompetent adult population. Eur J Neurol 2008;15:995–7.
[10] Pollak L, Dovrat S, Book M, Mendelson E, Weinberger M. Varicella zoster vs. herpes simplex meningoencephalitis in the PCR era. A single center study. J Neurol Sci 2012;314:29–36.
[11] Kupila L, Vuorinen T, Vainionpaa R, Hukkanen V, Marttila RJ, Kotilainen P. Etiology of aseptic meningitis and encephalitis in an adult population. Neurology 2006;66:75–80.
[12] Taylor WR, Nguyen K, Nguyen D, et al. The spectrum of central nervous system infections in an adult referral hospital in Hanoi, Vietnam. PLoS One 2012;7:e42099.
[13] Becerra JC, Sieber R, Martinetti G, Costa ST, Meylan P, Bernasconi E. Infection of the central nervous system caused by varicella zoster virus reactivation: a retrospective case series study. Int J Infect Dis 2013;17:e529–34.
[14] Skripuletz T, Pars K, Schulte A, et al. Varicella zoster virus infections in neurological patients: a clinical study. BMC Infect Dis 2018;18:238.
[15] Ak AK, Mendez MD. Herpes Simplex Encephalitis. Treasure Island, FL: StatPearls; 2021. https://www.ncbi.nlm.nih.gov/pubmed/32491575.
[16] Ai J, Xie Z, Liu G, et al. Etiology and prognosis of acute viral encephalitis and meningitis in Chinese children: a multicentre prospective study. BMC Infect Dis 2017;17:494.
[17] Roos KL, Tyler KL. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. Acute meningitis. Harrison's Principles of Internal Medicine, 20e New York, NY: McGraw-Hill Education; 2018.
[18] Agarwal AK, Bansal S, Nand V. A hospital based study on estimation of adenosine deaminase activity (ADA) in cerebrospinal fluid (CSF) in various types of meningitis. J Clin Diagn Res 2014;8:73–6.
[19] Gupta BK, Bharat A, Debapriya B, Baruah H. Adenosine deaminase levels in CSF of tuberculous meningitis patients. J Clin Med Res 2010;2:220–4.
[20] Liamis G, Milionis HJ, Elisaf M. Hyponatremia in patients with infectious diseases. J Infect 2011;63:327–35.
[21] Ray P, Badarou-Acossi G, Viallon A, et al. Accuracy of the cerebrospinal fluid results to differentiate bacterial from non bacterial meningitis, in case of negative gram-stained smear. Am J Emerg Med 2007;25:179–84.
[22] Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. N Engl J Med 2000;342:635–45.
[23] Mitchell BM, Bloom DC, Cohrs RJ, Gilden DH, Kennedy PG. Herpes simplex virus-1 and varicella-zoster virus latency in ganglia. J Neurovirol 2003;9:194–204.
[24] Hong HL, Lee EM, Sung H, Kang JK, Lee SA, Choi SH. Clinical features, outcomes, and cerebrospinal fluid findings in adult patients with central nervous system (CNS) infections caused by varicella-zoster virus: comparison with enterovirus CNS infections. J Med Virol 2014;86:2049–54.
[25] Koskiniemi M, Piiparinen H, Rantalaiho T, et al. Acute central nervous system complications in varicella zoster virus infections. J Clin Virol 2002;25:293–301.
[26] Pahud BA, Glaser CA, Dekker CL, Arvin AM, Schmid DS. Varicella zoster disease of the central nervous system: epidemiological, clinical, and laboratory features 10 years after the introduction of the varicella vaccine. J Infect Dis 2011;203:316–23.
[27] Singh TD, Fugate JE, Hocker S, Wijdicks EFM, Aksamit AJJr, Rabinstein AA. Predictors of outcome in HSV encephalitis. J Neurol 2016;263:277–89.
[28] Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303–27.
[29] Herlin LK, Hansen KS, Bodilsen J, et al. Varicella zoster virus encephalitis in Denmark from 2015 to 2019 – a nationwide prospective cohort study. Clin Infect Dis 2021;72:1192–9.
[30] Ganesh A, Kashani N, Bal SS, Jenkins J, Yeung MMC. Teaching neuroimages: varicella-zoster virus-related hemorrhagic encephalomyelitis. Neurology 2018;90:e1360–1.
[31] Salovin A, Glanzman J, Roslin K, Armangue T, Lynch DR, Panzer JA. Anti-NMDA receptor encephalitis and nonencephalitic HSV-1 infection. Neurol Neuroimmunol Neuroinflamm 2018;5:e458.